Remarks

The presently claimed invention features purified polypeptides comprising an amino acid sequence that is at least 70% identical to SEQ ID NO:3 (an *M. incognita* malate dehydrogenase). The presently claimed polypeptides have malate dehydrogenase activity.

Rejections Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected claims 1-3 as 9 as allegedly failing to meet the written description requirement of 35 U.S.C. §112, first paragraph.

Present claim 1 is drawn to a purified polypeptide that: 1) comprises an amino acid sequence that is at least 70% identical to SEQ ID NO:3 (an *M. incognita* malate dehydrogenase); and 2) has malate dehydrogenase activity. Malate dehydrogenase (MDH) is a tricarboxylic acid cycle enzyme that both reduces oxaloacetate to malate while oxidizing NADH to NAD and catalyzes the reverse reaction (oxidation of malate to oxaloacetate and reduction of NAD to NADH). The present specification provides a detailed description of an *in vitro* assay that can be used to assess the ability of a polypeptide to catalyze the conversion of oxaloacetate to malate (see page 36 of the specification). The specification also provides a detailed description of an *in vitro* assay that can be used to assess the ability of a polypeptide to catalyze the conversion of malate to oxaloacetate (see pages 36-37 of the specification). Thus, the specification provides two assays that can be used to determine whether a polypeptide, e.g., a polypeptide that comprises an amino acid sequence that is least 90% identical to SEQ ID NO:3 has malate dehydrogenase activity.

In *Regents of the University of California v. Eli Lilly & Co.*, the Court of Appeals for Federal Circuit held that an adequate written description of genetic material "requires a precise definition, such as by structure, formula, chemical name, or physical properties." 119 F.3d at 1563. The presently claimed nucleic acid molecules are defined by sequence (claim 4) or by sequence combined with function (claims 1-3). Thus, the present claims meet the written description requirement as articulated by the court in *Eli Lilly*.

The Synopsis of Written Description Guidelines published by the United States Patent and Trademark Office (the "Guidelines") includes an example of a claim drawn to a protein defined by sequence (percent identity to a reference sequence) and function (ability to catalyze a particular reaction) and supported by a specification disclosing an assay for the specified function. The Guidelines state that such claims can meet the written description requirement. Here, the polypeptides of claims 1-3 are drawn to polypeptides defined by sequence (percent identity a reference sequence, SEQ ID NO:3) and a function (malate dehydrogenase activity). These claims are supported by a specification disclosing two assays for the specified function. Thus, it is Applicants' position that the present claims meet the written description requirement as articulated in the prevailing case law and consistent with the USPTO's own guidelines.

The Examiner stated that SEQ ID NO:3 and SEQ ID NO:4 have different substrate specificity and used this a basis for arguing that previously pending claim 9 fails to meet the written description requirement.

> Claim 9 is drawn to a polypeptide that is 70% identical to SEQ ID NO:3 having MDH (malate dehydrogenase) activity. Even though MDH1 (SEQ ID NO:3) and MDH2 (SEQ ID NO:4) were isolated from *M. incognita* and share greater than 98% homology, the two resulting malate dehydrogenases have different substrate specificity. The specification does not disclose which amino acids impart a polypeptide as MD1 or MDH2. Therefore, based in the instant diclosure, it is unpredictable whether a polypeptide has MDH1 or MDH2 activity.

Applicants do not understand the Examiner's basis for asserting that SEQ ID NO:3 and SEQ ID NO:4 have "different substrate specificity". Applicants have not asserted that they have different substrate specificity. SEQ ID NO:3 is similar to codons 11-201 of *C. elegans* MDH1 (GenBank® accession number T20396; GI:7500583) and SEQ ID NO:4 is similar to codons 46-234 of *C. elegans* MDH2 (GenBank® accession number T18570; GI:7511561). Both *C. elegans* MDH1 and *C. elegans* MDH2 are malate dehydrogenases, and both can catalyze the conversion of oxaloacetate to malate and the conversion of malate to oxaloacetate. They are understood to both use the same substrates, although they are located in different subcellular compartments. The Examiner has not set forth any factual basis for concluding that that SEQ ID NO:3 and SEQ

IS NO:4 differ in substrate specificity, and it is not appropriate to assert that the claims fail to meet the written description requirement based on the alleged difference in substrate specificity between SEQ ID NO:3 and SEQ IS NO:4.

In view of the forgoing, Applicants respectfully submit that the rejection based on the written description requirement of 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected previously pending claims 1-3 and 9 as allegedly failing to failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

Given the teachings of the specification, one skilled in the art could make and use the nucleic acids without undue experimentation because the specification teaches one skilled in the art how to identify nucleic acid molecules encoding biologically active polypeptides. The Court of Appeals for the Federal Circuit has identified eight factors that must be considered in determining whether undue experimentation would be required to practice a claimed invention: "(1) the quantity of experimentation necessary, (2) the amount and direction of guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988).

With respect to the relative skill in the art, it is clear that the relative skill in art of generating variant polypeptides is very high. For example, those skilled in the art are aware of various random mutagenesis protocols can be used to create libraries of clones encoding variant polypeptides.

With respect to the guidance provided by the specification, the Examiner argues that specification does not provide sufficient guidance to enable one of ordinary skill in that art to identify functional polypeptides within the scope of the claims. The Examiner argues that the specification does not provide

> "(A) regions of the malate dehyrogenase which may be modified without effecting its activity; (B) the general tolerance of to [the malate dehydrogenase] to

> modification and extent of such tolerance; (C) a rationale and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (D) the specification provide insufficient guidance as to which of the essentially infinite possible choices is likely to be successful."

Applicants disagree with the Examiner's assertion that the specification does not provide sufficient guidance regarding which regions of MDH are important for activity and which amino acid substitutions are likely to be functional. The specification provides the amino acid sequences of four different MDH proteins (*C. elegans* MDH1, *C. elegans* MDH2, SEQ ID NO:3, and SEQ ID NO:4). Figure 3 of the specification (copy attached as Exhibit A) provides an alignment of amino acid sequence of these four different MDH proteins. As can be seen from the Figure 3, certain amino acids are conserved among the four proteins, others are conserved among three of the four proteins, and still others are conserved between two of the proteins. The sequence alignment of Figure 3 provides ample guidance to those of ordinary skill in art in creating functional polypeptides within the claims. Of course, in many case it is desirable to test the proteins for functional activity using one of the MDH assays described in the specification.

With respect to the absence or presence of working examples, the specification provides working examples of two *M. incognita* MDH proteins (SEQ ID NO:3 and SEQ ID NO:4).

Regarding the breadth of the claims, it is Applicants' position that the claims are not excessively broad encompassing as they do nucleic acid molecules encoding polypeptides having at least 70% (80% or 90%) to a reference polypeptide (SEQ ID NO:3).

With respect to predictability, although it cannot always be predicted whether a given amino acid change will alter function, it is generally understood, despite some exceptions, that certain types of variants, e.g., those involving conservative amino acid substitutions are more likely to retain function. Moreover, the sequence alignment provided in Figure 3 of the application provides information that allows one to more predictably select functional polypeptides within the claims.

With respect to the amount of experimentation required, the guidance regarding conserved residues combined with the simple assays for MDH activity provided in the specification permit one to make and use the claimed invention without undue experimentation.

Consideration of the *Wands* factors leads to the conclusion that the specification enables one of ordinary skill in the art to make and to use the invention.

In view of the forgoing, Applicants respectfully request that the enablement rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner rejected previously pending claim 9 under 35 U.S.C. §112, second paragraph as allegedly indefinite. The Examiner objected to the phrase "MDH-like activity" as indefinite. Claim 9 has been cancelled. The newly added claims refer to "malate dehydrogenase activity". In view of the forgoing, Applicants respectfully request that the indefiniteness rejection under 35 U.S.C. §112, second paragraph be withdrawn.

Rejections Under 35 U.S.C. §102

The Examiner rejected claims 1-4 and 9 as allegedly anticipated by www.ss.jircas.affrc.go.jp ("the reference") According to the Examiner, a photograph of an electrophoresis gel within this alleged prior art publication discloses an MDH isolated from *M. incognita* that has an amino acid sequence that is at least 70% identical to SEQ ID NO:3.

Assuming, without conceding, that the internet page identified by the Examiner is a prior art publication under 35 U.S.C. §102(b)[1], it is not sufficient to anticipate the present claims because there is no evidence that the *M. incognita* MDH described in the reference is purified as required by the present claims. Moreover, even if the reference discloses purified *M. incognita* MDH, the reference does not anticipate the present claims because it is not enabling.

The claims are drawn to a "**purified** polypeptide comprising an amino acid sequence that is at least 70% identical to the amino acid sequence of SEQ ID NO:3, wherein the polypeptide

[1] The Examiner stated that the reference is no longer on the Internet, but that it is available through a Internet archive (The Wayback Machine) and was present on the Internet at least one year prior to the priority date of the present application. It is unclear to the Applicants how the Examiner identified the cited reference. The date on which this reference became available is also unclear to the Applicants. Thus, it is unclear whether one interested in the field of nematode proteins could have searched for and found the reference prior to the priority date of the present application.

has malate dehydrogenase activity" (emphasis added). The reference provided by the Examiner concerns the identification of novel nematode species by electrophoretic analysis of MDH and esterase. The reference depicts an electrophoresis gel with several lanes labeled "Mi" for *M. incognita*. Several bands are evident in each lane. Some of the bands are identified as MDH and others are identified as "Est" (presumably esterase). The reference provides absolutely no description of what material was loaded onto the gel. For all the reference discloses, the material loaded on the gel could be total *M. incognita* extract or whole plant extract. The reference does not state that MDH was partially or fully purified. Indeed the presence of esterase bands on the gel in the same lanes as the MDH bands makes it clear that the MDH is not purified. The reference does not describe how the bands on the gel were visualized. In short, there is absolutely no evidence that the purported MDH is purified as required by the claims. Thus, the reference cannot anticipate the present claims.

It is quite possible that the material identified in the reference as MDH is not at all purified. There are published techniques for the identification of nematode species by electrophoretic analysis of MDH and esterase. For example, Cap et al. (*Electrophoresis* 13:295, 1992; Exhibit B) describes a method for identifying nematode species that involves macerating a single intact nematode in extracting buffer and then loading the extract on a gel. The gel is first stained using an enzymatic assay for MDH activity and then stained with a enzymatic assay for esterase activity. The bands identified as MDH and bands identified as esterase appear on the resulting stained gel (see Figure 3 of Cap et al.), yet is it clear that the bands cannot represent purified MDH or purified esterase since the gel was loaded with total nematode extract. The MDH band may represent scores of proteins, one of which is MDH. Thus, not only is there no evidence that the MDH in the reference provided by the Examiner is purified, there is ample reason to conclude that it is not purified.

Even assuming, without conceding, that the reference cited by the Examiner discloses purified MDH, it cannot anticipate the present claims because it is not enabling. It does not provide the even the slightest suggestion as to how to material loaded on the gel was prepared, the type of gel used, the running conditions for the gel, or how the MDH was visualized. One

skilled in the art could prepare purified *M. incognita* MDH based on the teachings of the reference provided by the Examiner. "[A] §102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it.'" *Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.* 804 F.2d 659, 664 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 933 (1987). Because the reference provided by the Examiner is not enabling, it cannot anticipate the present claim even if it does disclose purified MDH.

In view of the forgoing, Applicants respectfully request that the rejections under 35 U.S.C. §102(b) be withdrawn.

Enclosed is a Petition for Extension of Time with the appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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